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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/015,948	12/11/2001	Keith D. Allen	R-605	2942

7590 11/19/2003

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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	10/015,948	ALLEN ET AL.	
	Examin r	Art Unit	
	Thái-An N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) *1, 2, 10-13, 29-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-9 and 14-28* is/are rejected.

7)☒ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7/9/02* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-38 are pending. Claims 1, 2, 10-13 and 29-38 are withdrawn. Claims 3-9 and 14-28 are under current examination.

Election/Restrictions

Claims 1, 2, 10-13 and 29-38 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected groups, there being no allowable generic or linking claim. Election was made **without** traverse in the paper filed 7/31/03.

Applicant's election without traverse of Group II [claims 3-9 and 14-28] in the paper filed 7/31/03 is acknowledged.

Information Disclosure Statement

The Information Disclosure Statement, filed July 9, 2002, has been considered.

Claim Objections

Claim 9 is objected to because the claim is dependent upon a non-elected claim. The claim should be written in an independent form.

Claim Rejections - 35 USC § 101/112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3-9 and 14-28 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well-established utility.

The claims are directed to transgenic mice and methods of producing transgenic mice comprising a disruption in an adrenocorticotropin receptor [ACTHR] gene and cells derived from the transgenic mice.

The specification teaches methods of generation knockout mice and cells comprising a disruption in the ACTHR gene. The knockout mice generated by introducing a ACTHR targeting construct into mouse ES cells to generate chimeric mice, which were then bred to produce heterozygotes which were then backcrossed to generate ACTHR homozygous knockout mice. See Example 1. The specification teaches that the homozygous knockout mice of the invention exhibit a phenotype of hypoplasia of the adrenal gland, abnormalities in brown adipose tissue [particularly decreased cytoplasmic lipid vacuolation of brown adipose tissue], decreased body fat percentage, an increased susceptibility to seizure, hyperactivity, and an anti-

depressant phenotype, as seen by a decrease in total time spent immobile in the tail suspension test. See pp. 3-4 and Examples 2-5 of the specification. The specification teaches that the cell- and animal-based systems can be used as models for diseases and then used in assays to screen strategies designed to identify agents, such as compounds capable of ameliorating disease symptoms. See p. 19, lines 19-27.

The specification has provided general teachings that the claimed transgenic mice may be used to identify agents that affect a phenotype related to the mice [see p. 20, lines 16-20, for example. As such, the asserted utility of the claimed transgenic mice is for screening agents that may affect the phenotype of hypoplasia of the adrenal gland, abnormalities in brown adipose tissue [particularly decreased cytoplasmic lipid vacuolation of brown adipose tissue], decreased body fat percentage, an increased susceptibility to seizure, hyperactivity, and an anti-depressant phenotype, as seen by a decrease in total time spent immobile in the tail suspension test. The asserted utility does not appear credible to the skilled artisan because the evidence of record has not provided a correlation between an ACTHR gene and these phenotypes and any disease or disorder. As the evidence of record has not provided a correlation between these phenotypes and any disease or disorder, the utility of identifying agents that affect the described phenotypes is not apparent. Furthermore, the evidence of record has not provided any other utilities for the claimed transgenic mouse that are specific, substantial and credible.

The specification teaches that the asserted utility of the claimed transgenic mouse and cells derived therefrom would be as a model for disease. The specification fails to correlate the phenotype [hypoplasia of the adrenal gland, abnormalities in brown adipose tissue [particularly decreased cytoplasmic lipid vacuolation of brown adipose tissue], decreased body fat percentage, an increased susceptibility to seizure, hyperactivity, and an anti-depressant phenotype, as seen by a decrease in total time spent immobile in the tail suspension test] of the claimed transgenic mice with any disease or disorder. These phenotypes are not found to be associated with any disease or condition.

Furthermore, the specification and art teach that mutations in ACTHR result in FGD. Weber *et al.* [Reference 7 of Applicants' IDS filed 7/9/02] teach that FGD is, "[C]haracterized by the presence of elevated circulating ACTH levels, but normal mineralocorticoid production. Patients usually present in early childhood with one or more of the following: hyperpigmentation, hypoglycemic episodes, failure to thrive, and frequent and severe infections. However, age of onset of symptoms and clinical severity of the disease vary considerably between cases, suggesting a heterogeneous genetic origin." See p. 65, 1st column, 1st ¶. If Applicants intend for the claimed transgenic mice to be disease models for FGD, there is no correlation or nexus provided by the specification to show that the mice exhibit any phenotype associated with FGD.

Accordingly, neither the specification, nor any evidence of record, provide a correlation or nexus between the phenotypes associated with the homozygous knockout ACTH mice and any disease or disorder, leaving the skilled artisan to speculate and investigate further uses for the claimed transgenic mice.

Claims 3-9 and 14-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Specifically, since the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention, claims 3-9 and 14-28 lack enablement.

Furthermore, the mere capability to perform gene transfer in a mouse is not enabling because a desired phenotype cannot be predictably achieved by simply introducing transgene constructs of the types recited in the claims. While gene transfer techniques are well developed for a number of species, and in particular, the mouse, methods for achieving the desired level of transgene expression in appropriate tissues are less well established. The introduction of DNA into the mammalian genome can ordinarily be achieved most reliably by microinjection or

retrovirus-mediated gene transfer. However, the state of the art for transgenics is unpredictable because the method of gene transfer typically relies on random integration of the transgene construct. Insertional inactivation of endogenous genes and position effects [see Ryan *et al.*, **Sem. Neph.** 22:154-160, 2002] can dramatically influence the phenotype of the resultant transgenic animal. Ryan *et al.* state that methods such as pronuclear injection or gene targeting by homologous recombination are still limited by several unpredictabilities, including differences in transgene copy number and position of integration into the genome. Furthermore, Ryan *et al.* state "The location of integration can have dramatic effects on the expression of a transgene. Called the position effect, transcriptional regulatory sequences at or near the insertion site can strongly influence your transgene, even impart a new set of instructions." [See p. 155, 2nd column].

Additionally, the state of the art of generation of knockout animals is found to be unpredictable. For example, the knockout art teaches that the disruption of a different exon of the same gene may <u>not</u> result in the anticipated phenotype. See Moreadith et al. (Journal of Molecular Medicine, 1997) who support phenotypic unpredictability in knockout mice. In particular, Moreadith et al. discuss that gene targeting at a particular loci is unpredictable with respect to the resulting phenotype since often the generation of knockout mice, in many instances, changes the prevailing notions regarding the functions of the encoded proteins. For example, Moreadith et al. report that gene targeting at the endothelin loci led to the

creation of mice with Hirschsprung's disease instead of the anticipated phenotype (abnormal control of blood pressure). See page 208, column 2, 2nd paragraph.

The breadth of the claimed invention encompasses chimeric, heterozygous and homozygous animals. The specification teaches homozygous ACTHR knockout mice that exhibit a phenotype of hypoplasia of the adrenal gland, abnormalities in brown adipose tissue [particularly decreased cytoplasmic lipid vacuolation of brown adipose tissue], decreased body fat percentage, an increased susceptibility to seizure, hyperactivity, and an anti-depressant phenotype, as seen by a decrease in total time spent immobile in the tail suspension test. The specification teaches that the animals of the instant invention can be used as models for diseases. See p. 19, lines 19-27. However, the specification fails to teach a phenotype associated with the chimeric or heterozygous animals comprising a disruption in an ACTHR gene, as encompassed by the claims. As such, one of skill in the art would not know how to use the chimeric mice or heterozygous mice as encompassed by the claims because they have no disclosed phenotype that would make them useful as disease models.

Given that specific phenotypic alterations cannot be predictably achieved by merely transferring a gene of interest into an animal, specific guidance must be provided to enable the instant invention. The specification must teach those skilled in the art how to make and use the full scope of the instant invention. The specification teaches that the claimed transgenic non-human animals, and

transgenic mice would be used as models for disease [see p. 19, lines 19-27]; however, the specification does not enable this use. In absence of a disclosure of a transgenic animal exhibiting an appropriate phenotype, undue experimentation would have been required to make and use the claimed transgenic non-human animals. The specification specifically discloses the disruption of the ACTHR gene and that the transgenic animals of the invention may be used as models for diseases, disorders, or conditions associated with phenotypes relating to a disruption in the ACTHR gene [see pp. 20-21, bridging sentence]; however, the phenotypes as taught by the specification do not correlate to an ACTHR disease.

The breadth of the claimed invention is directed to the generation of transgenic non-human animals comprising a targeted disruption in the ACTHR gene, which requires embryonic stem [ES] cells. The state of the art is such that ES cell technology is generally limited to the mouse system at present, and that only "putative" ES cells exist for other species (see Moreadith *et al.*, **J. Mol. Med.**, 1997, p. 214, S*ummary*). Note that "putative" ES cells lack a demonstration of the cell to give rise to germline tissue or the whole animal, a demonstration which is an art-recognized property of ES cells. Moreadith *et al.* supports this observation as they discuss the historical perspective of mouse ES cells as follows:

"The stage was set-one could grow normal, diploid ES cells in culture for multiple passages without loss of the ability to contribute to normal development. Furthermore, the cells contributed to the development of gametes at a high

frequency (germline competence) and the haploid genomes of these cells were transmitted to the next generation. Thus, the introduction of mutations in these cells offered the possibility of producing mice with a predetermined genotype."

Such a demonstration has not been provided by the specification or the prior art with regard to the generation of any species of animal ES cells, other than the mouse, which can give rise to the germline tissue of a developing animal. In addition, prior to the time of filing, Mullins *et al.* (**Journal of Clinical Investigation**, 1996) report that "although to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated." (page 1558, column 2, first paragraph). As the claims are drawn to methods involving the manipulation of animal embryonic stem (ES), and particularly since the subject matter of the specification and the claimed invention encompasses the use of such cells for the generation of a transgenic animal, the state of the art supports that only mouse ES cells were available for use for production of transgenic mice.

Note that claim 5 is directed to a murine ES cell. The term "murine" encompasses both mice and rats. As stated above, the state of the art only supports that mouse ES cells were available for the generation of knockout mice.

This is further supported by Pera *et al.* [**Journal of Cell Science** 113: 5-10 (2000)] who present the generic criteria for pluripotent ES or EG cells [see p. 6, 2nd

column] and state that, "Thus far, only mouse EG or ES cells meet these generic criteria." [See p. 6, 2nd column, last paragraph].

Accordingly, in view of the quantity of experimentation necessary for the production and use of non-human transgenic animals comprising a disruption in an ACTHR gene, the lack of direction or guidance, as well as working examples, provided by the specification for the production and use of non-human transgenic animals, for the breadth claimed, the unpredictable and undeveloped state of the art for the production of transgenic knockout non-human animals, particularly with respect to the unpredictable nature of the phenotypic effect, and the breadth of the claims encompassing all non-human animals, it would have required undue experimentation for one of skill in the art to make and use the claimed non-human transgenic animals, cells, and methods of using the same.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the

subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 3-9, 14 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Capecchi [**Scientific American**, 1994, 270:34-41] when taken with Kubo *et al.* [Reference 1 of Applicant's IDS filed 7/9/02].

Capecchi teaches knockout technology applied to mice, specifically with respect to the disruption of the *Hox*A-3 gene and as a method of producing the same, applies to determining the *in vivo* biological function of any known gene of interest [see p. 37, col. 1-2, bridging ¶ and Figures pp. 36-37]. For example, Capecchi discloses the applicability of gene targeting to many other genes, so that a correlation can be drawn between the malfunctioning gene to the manifestation of disease [see p. 41, col. 2, 2nd full paragraph]. Capecchi further discloses the essential components of a targeting vector [p. 38, col. 3, and p. 39, col. 1-2], and the steps involved for targeted gene replacement in ES cells as well as in mice [see p. 36-39 and diagrams]. Capecchi differs from the claimed invention in that the targeting construct does not contain flanking nucleotide sequences which

homologous recombine with the mouse ACTHR gene. However, prior to the time the claimed invention was made, Kubo teach the cloning of the mouse ACTHR gene. See Figure 1.

Note that absent any phenotypic requirements of the claimed transgenic mice, the combination of the cited prior art is sufficient to make obvious the invention. Further note that it would be well-known in the art that the disruption of any gene of interest, at any particular exon would have a reasonable expectation of success in the decreased expression of that particular gene.

Accordingly, in view of the combined teachings, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the knockout technology of Capecchi by use of a targeting vector for the disruption of the known mouse ACTHR gene in a mouse with a reasonable expectation of success. One of ordinary skill would have been sufficiently motivated to make such a modification, as it was an art-recognized goal to determine the physiological role of a gene of interest by the generation of a knockout mouse, as supported by Capecchi who teach that the generation of mouse models will allow for the observation of effect of a knocking out a particular gene on disease phenotypes. See p. 41, 2nd column, 2nd ¶.

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear and convincing evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thái-An N. Ton whose telephone number is (703) 305-1019. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the examiner be unavailable, inquiries should be directed to Deborah Reynolds, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-4051. Any administrative or procedural questions should be directed to William Phillips, Patent Analyst, at (703) 305-3482. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703)-872-9306.

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